Symposium - Psoriasis

Novel drug delivery systems in topical treatment of psoriasis: Rigors and vigors

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ABSTRACT

Psoriasis is a chronic inflammatory skin disorder that may drastically impair the quality of life of a patient. Among the various modes of treatments for psoriasis, topical therapy is most commonly used in majority of patients. The topical formulations based on conventional excipients could serve the purpose only to a limited extent. With the advent of newer biocompatible and biodegradable materials like phospholipids, and cutting-edge drug delivery technologies like liposomes, solid lipid nanoparticles (SLNs), microemulsions, and nanoemulsions, the possibility to improve the efficacy and safety of the topical products has increased manifold. Improved understanding of the dermal delivery aspects and that of designing and developing diverse carrier systems have brought in further novelty in this approach. Substantial efforts and the consequent publications, patents and product development studies on the subject are the matter of interest and review of this article. However, majority of the work is related to the preclinical studies and demands further clinical assessment in psoriasis patients.

Key words: Dermal drug delivery, Liposomes, Microemulsions, Nanoparticles, Phospholipids, Vesicles

INTRODUCTION

Topical therapy is the mainstay of treatment for mild to moderate psoriasis and serves as a useful adjunct support to systemic therapy in severe disease. However, efficacy and compliance to topical therapy in psoriasis have been a major concern. Approximately, 70% of the psoriasis patients in three large surveys were found to be unsatisfied or moderately satisfied with their current treatment.[1] Lack of effective delivery of drugs and undesirable skin interactions of the topical treatments are the main reasons for patient noncompliance.[2] Nevertheless, newer developments in the formulation approaches have raised hopes in making topical therapy more useful and acceptable.[3] The present paper endeavors to review the overall developments in the field of Novel Drug Delivery Systems (NDDS) pertaining to the topical treatment of psoriasis.

NOVEL DRUG DELIVERY SYSTEMS

In search of safe and effective therapy, the development of new drugs has been the common practice historically. However, it involved a long gestation period in terms of time, efforts, and huge cost. Later on, it was realized that the issues pertaining to efficacy and safety are largely influenced by the distribution of the drug within the biological system, as there is appreciable deviation from the desired site of action, i.e., the target site. In fact, Nobel laureate, Sir Paul Ehlrich in 1905 envisioned the drug molecules as "magic-bullets" to hit the specific target site to attain the absolute efficacy and safety.[4] This objective, hitherto un-accomplished gave way to an alternate approach of drug delivery, wherein the carrier systems were used to deliver the molecules to specific receptor sites without afflicting the normal tissues and organs of the body. Interestingly, it turned out to be a transformation of the original idea of "magic-bullets" to that of the "magic-guns." The fundamentals lie in hosting the drug in carefully designed carriers to bring favorable change(s) in its surrounding microenvironment, and consequently, its delivery. It is

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the modification(s) in physicochemical characteristics of the molecules and in the barrier properties of the biological membranes at various locations, which lead to improved transportation of drugs toward the diseased locations. Further, it improves the chances of the availability of the drug at the specific receptor site and enhances drug–receptor interaction through mediation of specialized composition and design of the carrier systems. All these factors tend to potentiate the degree of pharmacodynamic response, the safety and patient compliance being the immediate benefits.

The novel carriers have been exploited through almost all the routes of administration. However, the topical route has been adjudged as one of the most relevant to treat dermatological disorders more effectively. In contrast to the conventional formulations based on creams and ointments, these novel dermatological systems are different in their composition and constructs including their exterior and interior design.[5,6] Various pharmaceutical and dermatological variables influence the choice of the system as per the demand of the drug and disease. Phospholipids represent a special class of surfactants with two long fatty acid chains (lipid region) and a bulky polar head (hydrophilic region) linked with phosphor-group on glycerol as the backbone. The unique structural features allow phospholipids to interact with water to form well-organized supra-structures like liposomes. The variation in composition and methods influences the nature of such self-assembled supra-structures in terms of their shape, design, size, and surface properties. This leads to different classes of carriers, viz. liposomes,[7-9] transfersomes, micro and nanoemulsions,[10-12] niosomes,[13,14] dendrimers[15] invasomes[16,17] solid lipid nanoparticles (SLNs),[18-22] and nano lipid carriers (NLCs)[20,21,23,24] [Table 1]. These carrier systems provide the entrapment opportunities to the drug molecules within their interior locations as per their fitment of steric and physicochemical properties. Association of drugs with carriers is normally noncovalent, based on collective strength of weak binding forces. Many newer carriers are evolving with the advent of technology and the demand of targeted delivery like ethosomes, emulsomes, magnetic nanoparticles, resealed erythrosomes and bilosomes.

Apart from projected advantages, the novel carriers have associated drawbacks of high cost of excepients, need of expertise in the production of such carriers, stability, and evaluation issues.

Table 1: Various colloidal carriers employed during topical delivery of drugs

Drug delivery carrier systems	Description
Liposomes	Vesicular carriers composed of bilayers of phospholipid molecules and enclosed water in these bilayers
Niosomes	Vesicular carriers composed of non-ionic surfactants instead of phospholipids
Microemulsions	Thermodynamically stable, isotopically clear and transparent carriers composed of oil, aqueous phase and surfactant(s). They are supersolvents.
Lipid emulsions	Micro- and nano-emulsions containing phospholipids as one of their surfactants
Transfersomes, flexible membrane vesicles	Liposomes with edge activators, highly deformable, reported to penetrate stratum corneum as such
Ethosomes	Liposomal systems comprising of high alcohol content, flexible vesicles, high drug loading
Solid lipid nanoparticles	Nanocolloids composed of drug loaded in solid lipid particles
Emulsomes	Nanocarriers with solid lipid core along with bilayers of phospholipids
Nanolipid carriers	Nanocolloids composed of drug loaded in lipid core composed of both solid and liquid lipids
Invasomes	Liposomes containing penetration enhancers
Dendrimers	Repeatedly branched, roughly spherical large molecules also used for drug delivery

Figure 1 illustrates the pictorial representation of such interactions of the carriers with skin.[7] The novel carrier systems are versatile and flexible in handling the various issues associated with the drug and thus, possess high potential for better patient compliance. Table 2 enumerates the meritorious roles of NDDS in topical therapy. Various attempts have been made

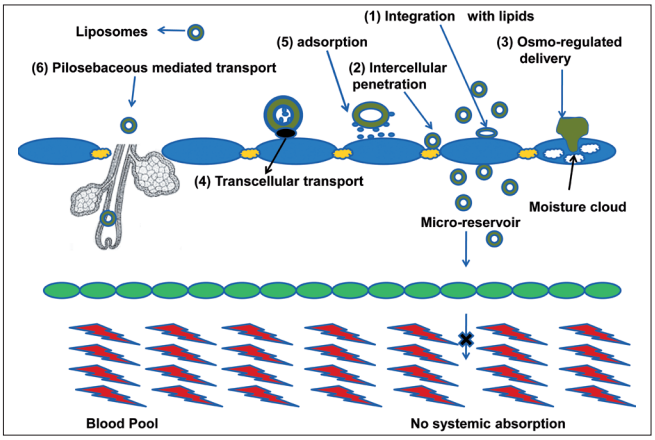

Figure 1: Various mechanisms of penetration of drug-loaded liposomes across skin

in the recent past in reporting many studies for the delivery of various drugs employing novel colloidal carriers. Table 3 enlists selected instances.[25-64]

CHALLENGES IN TOPICAL DELIVERY OF DRUGS IN PSORIATIC SKIN

According to the studies reported recently, stratum corneum (SC) is not an inert layer, but an "active-wall," which opposes the penetration of xenobiotics.[4]

Table 2: Role of Novel drug delivery systems

- Use of versatile carriers
- Imparting protection to the molecules
- Biocompatibility of the systems
- Passive targeting
- Loading a variety of drugs
- Modifications in the physicochemical properties

Though no molecule can readily and fully pass through this membrane, yet it allows penetration of nearly all the materials to some extent. It is also vivid that the major route of penetration across the SC is the intercellular lipids.[4] The state of hydration of SC is one of the most important factors in determining the rate of percutaneous absorption of a given solute. The level of hydration is a function of the water concentration gradient between the dermis and the surface of the skin as well as the ability of the SC to "bind" water.[5] Delivery of solutes through the skin is associated with a number of difficulties as shown in Table 4.

"Rigidization" of psoriatic skin has been attributed to a rise in the levels of cholesterol and fall in the levels of ceramides.[6] Apart from this, normal moisturizing factors (NMFs) like water are almost absent in the psoriatic skin. As a result of various factors, targeting the psoriatic tissues using topical route poses a big

Table 3: List of drugs (topical) encapsulated in various carrier systems[25-64]

Drugs	Indication	Type of Drug Delivery System
Cyclosporin A	Allergic skin disorders (atopic dermatitis)	Solid lipid nanoparticles[25]
Calcineurin inhibitors	Prevent DNA photodamage	Liposomes[26]
Amphotericin B	Fungal infection	Liposomes[27]
Fluconazole	Fungal infection	Liposomal gel[28]
Fluconazole	Fungal infection	Ethosomes[29]
NB-002	Fungal infection	Nanoemulsion[30]
Ketoconazole	Fungal infection	Liposomes[31]
Ciclopirox Olamine	Fungal infection	Liposomal gel[32]
Methotrexate	Psoriasis	Liposomes[33]
Methotrexate	Psoriasis	Ethosomes[34]
Methotraxate	Psoriasis	Niosomes[35]
Methotrexate	Psoriasis	Liposomes[36]
Temoporfin	Photodynamic therapy- psoriasis	Liposomal gels[37]
Dithranol	Psoriasis	Liposomes and niosomes[38-41]
Coal tar	Psoriasis	Lecithinized coal tar formulation[42] Lipid-coated microparticles[43]
Tacrolimus	Psoriasis	Nanoparticles and liposomes[44,45]
Cetirizine	Pruritus	Liposomes[46]
Butorphanol	Pruritus	Liposomes[47]
Lauric acid	Inflammatory acne	Liposomes[48]
Azelaic acid	Acne	Liposomes and Ethosomes[49]
Tretinoin	Acne	Liposomal gel[50]
Benzyl peroxide	Acne	Liposomal gel[51]
Idoxuridine	Herpes simplex	Liposomal gel[52]
Dipotassium Glycyrrhizinate	Acute and chronic dermatitis	Liposomes[53]
Prednisolone	Allergic dermatitis	Magnetic liposomes[54]
Capsaicin	Musculoskeletal pain	Flexible membrane vesicles[55]
Nimesulide	Inflammation and pain	Liposomes[56]
Finasteride	Acne, androgenetic alopecia	Liposomes[57]
Corticosteroid	UV induced erythma	Skin-lipid liposomes[58]
	Corticosteroid-responsive dermatoses	Emollient foam formulation of clobetasol propionate[59]
Tamoxifen	Certain skin disorders	Liposomes[60,61]
Hydroxyzine	Skin Allergy	Liposomes[62]
Vitamin D analogues: Calcipotriol, tacalcitol, calcitriol	Antiparakeratosis function	Liposomes[63,64]

Table 4: Challenges for topical drug delivery

• Variability in percutaneouus absorption due to site, disease, age, etc.
• Skin "first-pass" metabolic effect
• Reservoir capacity of the skin
• Irritation potential and other toxicities due to drug
• Heterogeneity and inducibility of the skin in turn-over and metabolism
• Inadequate definition of bioequivalence criteria
• Incomplete understanding of technologies to facilitate or reduce percutaneous absorption

challenge. The intricacies of the topical delivery into the psoriatic skin have lately been proposed to be addressed by the lipoidal carrier systems, such as liposomes. The latter resolve the problem of lipid imbalance by imparting the unsaturated fatty acids like linoleic acid to restore the normal skin conditions.[4] Hence, these liposomal and allied carriers can result in an effective delivery of drugs across the psoriatic skin.[65]

Several topical therapeutic agents are available for the treatment of psoriasis. Nevertheless, none of them can be regarded as an ideal drug molecule. This may either be due to their inherent side effects or their improper incorporation in the conventional vehicles. It is a well-known fact that due to variation in the physicochemical characteristics of the carrier and of the active compounds used, the degree of drug absorption through skin may vary, and therefore, may be the drug efficacy. Hence, the carriers based on scientific approach can modify the physicochemical properties of the drugs and can help to decrease the intensity and frequency of side effects associated with these active moieties.[66] Formulations like gels, creams, ointments, and lotions are frequently used for the topical delivery of the antipsoriatic agents. However, these formulations are often not able to mask the drug-related issues causing obvious problems with patient acceptance and compliance [Table 5].[4,65,67] The topical delivery vehicle must be suitably designed and developed to attain the desirable attributes for use in extremely dehydrated and thickened psoriatic skin having lipid imbalance and sensitive to irritants.[10]

NOVEL DRUG DELIVERY SYSTEMS IN TOPICAL THERAPY FOR PSORIASIS

The NDDS with their unique advantageous features provide favorable skin interactions as desired in the diseased conditions like psoriasis. Considering the benefits, there have been several recent attempts to use the NDDS approach to improve the existing topical drug formulations in psoriasis. A brief account of the efforts presents here the current scenario.

Table 5: Common skin barrier problems in psoriasis

• Thickened inflamed skin lesions covered with scales
• Dry and natural moisturizing factor deficient skin
• Sensitive skin
• Tethered hairy skin
• Imbalance of skin lipids
• Excessive growth and aberrant differentiation of corneocytes

Dithranol

Dithranol, with a long history of use spanning over more than 100 years, is one of the most effective topical therapies in psoriasis. But in the existing form of products, it has not been fully accepted, mostly because of its irritation and staining properties. This made a long-standing demand on the researchers world wide to search for the modified molecule or formulation. It included enormous efforts as reflected in more than 1500 publications, patents and exclusive meetings on the dithranol per se. Various efforts like chemical modifications of the molecule, formulation changes, new treatment modifications or strategies and other miscellaneous approaches like short-contact therapy did not provide any definite solution.[68-70] Subsequent work on liposomal systems with dithranol led to the improvement in its skin penetration.[71] Agarwal *et al*. developed dithranol entrapped in liposomal and niosomal vesicles (0.5%) and found both of them superior to conventional formulation, while liposomes showed better results than niosomes employing mice skin. They found both of them superior to conventional formulation, while liposomes showed better results than niosomes.[38] Gidwani *et al*. in their patent application revealed the usefulness of mixed vesicular systems of dithranol with and without salicylic acid. The formulations, when tested on more than 12 patients for 4 weeks, proved to be effective and devoid of irritation and staining.[72]

The study on liposomal dithranol continued by Katare *et al*. resulted in the development of a product.[39-41,73,74] This product when tested clinically in an open label[41] as well as randomized double blind trials[40] showed that dithranol in greatly reduced doses (0.5%) in liposomes could clear the psoriasis

plaques to match that of 1.15% commercially available dithranol ointment.[40] The advantages of liposomal dithranol in terms of efficacy and compliance (nonirritancy and nonstaining) have been attributed to the ability of strategic liposomal formulation design [Figure 2]. In the latter form, the reactivity of drug is moderated to the desired level, while favorable drug–skin interactions as a result of membranous layers of liposomes do not allow for irritancy and deep staining of clothes.[39,40]

Methotrexate

Methotrexate (MTX) is the gold standard drug used systemically in psoriasis, though there are not many products available for its topical application. The key reason for this is its inability to penetrate adequately in the skin and get access to the target cells.[75,76] But of late, several formulations and delivery techniques have been employed in order to improve its delivery through skin. Strategies include the use of different penetration enhancers,[49,77] adhesive laminate tapes as occlusive covering,[78] physical techniques like iontophoresis,[79,80] and development of novel drug delivery vehicles. In a study of liposomal formulation of MTX conducted in six patients, it resulted in clearance of psoriasis lesions, while one patient recovered completely.[81] Further modified version of liposomes, i.e., deformable liposome was found to be quite superior to that of aqueous solution and normal liposomes *in vitro*.[33] In a double-blind placebo-controlled trial involving 40 psoriasis patients, niosomal systems in chitosan gel (0.25%) resulted in a better efficacy, tolerance, and patient compliance, when compared to a marketed formulation.[35] Another version of liposomal system containing ethanol, i.e., ethosomes, showed favorable skin permeation characteristics.[34] Trotta *et al.* developed oil in water (o/w) microemulsions of MTX having sixfold higher permeation flux than that from the corresponding solutions in mice skin.[82] Recently, MTX incorporated in a hydrogel formulation showed zero-order kinetic release and antipsoriatic activity.[36] This formulation was evaluated in 35 psoriasis patients and the application site was also irradiated with 80 J diode laser of wavelength 650 nm, thrice a week. During 8 months' follow-up, up to 60% of the patients treated with LMTX gel had no recurrence.[36] Solid lipid nanoparticles (SLN) of MTX have showed improved drug accumulation in human cadaver skin. This formulation was also investigated clinically on 24 psoriasis patients for 6 weeks period. The researchers reported that MTX SLN-gel significantly improved the therapeutic index in terms of average percent improvement in healing (APIH) of lesions and reduction in average score of degree of erythema and scaling.[83]

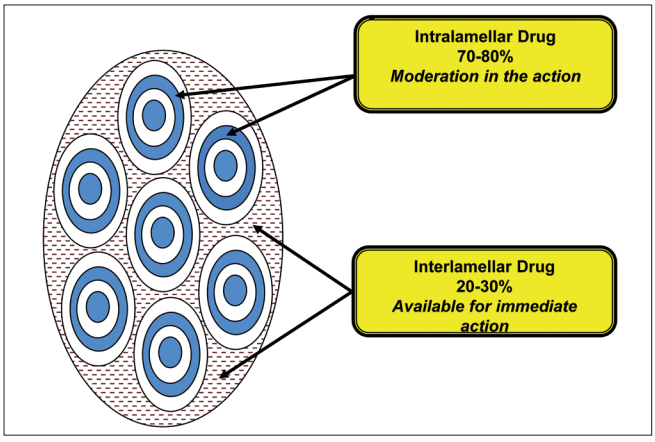

Figure 2: Inter- and Intralamellar distribution of dithranol in liposomal formulation

Retinoids

Tretinoin (TRE) is a widely used drug in the topical treatment of acne,[84,85] photo-aged skin,[85] psoriasis[86] and other skin disorders but unpleasant side effects often appear in the form of scaling, erythema, burning, and stinging. Several attempts have been made to incorporate the drug in various colloidal carriers. For instance, the drug has been incorporated into liposomes,[14,59] niosomes,[60-62] SLNs,[63] and nanocapsules.[64] These studies have been carried out in various animal models and reported to perform quite well. Safe iontophoretic tretinoin delivery is also reported in human volunteers.[87]

Tamoxifen

Tamoxifen (TAM), an anti-estrogen compound given systemically, has recently been figured as a useful agent in the treatment of certain skin specific disorders like psoriasis.[88,89] Enhanced epidermal transport of TAM employing different penetration enhancers has been reported.[90] Katare *et al.* (2004) developed TAM liposomes of multilamellar nature, which exhibited appreciably enhanced skin permeation as well as retention of drug molecules in the skin.[60,91]

Vitamin D-analogues

Vitamin D_3 analogues such as calcipotriol, maxacalcitol, tacalcitol, and calcitriol are the mainstay of treatment in mild-to-moderate plaque psoriasis. Local irritation is the most frequently noted side effect, which is managed by combining vitamin D_3 analogues with topical corticosteroids.[92] Lin *et al.* developed NLCs

loaded with both MTX and calcipotriol and reported enhanced drug permeation with limited skin irritation in animal models.[93] Prufer *et al*. incorporated 1,25-dihydroxyvitamin D_3 in liposomes and reported its superiority over un-encapsulated drug in efficacy as well as safety.[64]

Tacrolimus

Tacrolimus (FK506), an effective and well-tolerated immunosuppressant, has also found its importance in the treatment of chronic plaque-psoriasis. Various clinical trials of tacrolimus in chronic plaque-psoriasis have been conducted with the conventional topical formulations.[94-98] Only preclinical animal studies with liposomes and nanoparticles of tacrolimus have been reported with improved skin transport effect.[69-70]

Theophylline derivatives

Dyphylline, a derivative of theophylline, inactivates cyclic AMP (cAMP), and is, therefore, used in the management of psoriasis.[99] Touitou *et al*. (1992) reported significant increase in permeation of dyphylline across abdominal mice skin using liposomal systems, thus corroborating its promise in topical delivery.[100]

Levulinic acid derivatives

Topical photodynamic therapy (PDT) with 5-aminolevulinic acid (ALA), a second-generation photosensitizer is a treatment option for psoriasis covering large area.[101] The major limitation of this strategy, however, is the poor penetration of ALA into the skin lesions. Recently, Fang *et al*. developed ethosomal system for topical delivery of ALA to overcome its penetration problem. The said work significantly contributed in understanding of the behavior and outcome of penetration of hyperproliferative murine skin.[102]

Temoporfin

Temoporfin (mTHPC) is a very potent second-generation synthetic photosensitizer with high tumor selectivity on activation at 652 nm. However, due to low aqueous solubility and high lipophilicity, the drug is difficult to be delivered topically.[16] Considering this, Dragicevic-Curic *et al*. formulated a different type of vesicular systems (invasomes) which improved topical delivery of mTHPC indicating promising advantage for the photodynamic therapy.[16,17]

Corticosteroids

Cortecosteroids, one of the most frequently used classes of drugs in dermatology, have been in practice to treat psoriasis too, either alone or in combination with other drugs.[103,104] Korting *et al*. developed liposomes containing 0.039% betamethasone dipropionate (BDP) and compared it with a commercial propylene glycol gel containing 0.064% BDP in a double-blind, randomized, paired trial lasting 14 days in 10 patients with psoriasis vulgaris and eczema. This report documented improvement in case of eczema, but not in psoriasis.[105]

Psoralens

Psoralens, mainly employed in PUVA are 8-methoxypsoralen (8-MOP), 5-methoxypsoralen (5-MOP), and 4,5,8-trimethylpsoralen (TMP). Studies have shown that the application of an emulsion cream and a microemulsion of 8-MOP helps in localization of the drug. Baroli *et al*. developed microemulsions for topical delivery of 8-MOP at the target site and enhanced porcine skin accumulation of 8-MOP without systemic side effects.[106] Fang *et al*. developed nanoparticulate lipid-based drug carriers viz. SLNs and NLCs, with increased skin permeation and controlled release properties for psoralens.[107]

Terpenoids

Triptolide (TP), a diterpenoid triepoxide, is indicated in the clinical treatment of psoriasis via oral or intravenous route.[108] However, the clinical use of triptolide is limited because of its severe systemic toxicity profile. Mei *et al*. developed SLNs and microemulsions in order to explore their potential for the topical delivery of TP. The results indicated that these SLN dispersions and microemulsions could serve as efficient promoters for the TP penetrating into skin.[109] Chen *et al*. also developed microemulsions, and it showed an enhanced *in vitro* permeation through mouse skins compared to an aqueous solution with no obvious skin irritation. They also studied hydrogel microemulsion of TP and found improvement in its penetration.[110]

Cyclosporin A

Cyclosporin A (CsA) is used in the treatment of psoriasis by oral as well as topical route. Its high molecular weight (more than 500 Da) and limited cutaneous permeation are the key challenges for topical delivery.[111] Many attempts have been made to achieve localized site-specific immunosuppression using conventional topical formulations of CsA, e.g., at Novartis Research Centre (Vienna, Austria), but of without any avail.[112,113] Duncan *et al*. in a small double-

blind, vehicle-controlled trial reported significant improvement in psoriasis lesions treated with topical CsA formulation with penetration enhancer(s).[114] Guo *et al*. developed lecithin vesicular carriers for the transdermal delivery of CsA. They observed by *in vitro* permeation technique that the flexible vesicles are better carriers for dermal enhancement.[115] Ugazio *et al*. incorporated CsA in SLNs and proposed for the exploitation through various routes.[116] Boinpally *et al*. studied the effect of iontophoresis on topical delivery of CsA across human cadaver skin using lecithin-solubilized drug which resulted in appreciable drug transport across skin. Few reports demonstrated monoolein as penetration enhancer for the topical and transdermal delivery of CsA in various liquid crystalline systems.[117-119] Verma *et al*. reported increased transport of CsA across skin employing alcoholic liposomes.[120] Katare *et al*., demonstrated successful topical delivery of CsA through multicompartmental liposomes and microemulsified systems.[121,122] Liu *et al*. reported that 40% ethanol and 10% menthol shortened the lag time of the penetration of CsA into deeper skin layers.[123]

Coal tar

Some studies have been conducted on very old but highly useful drug, coal tar, using novel phospholipid structured topical formulation. This approach has been reported to be beneficial in meeting the challenges of skin irritation and staining on cloth and skin.[42] They also reported better anti-psoriatic activity of this novel formulation *vis-à-vis* the conventional formulation employing mouse tail model of psoriasis.[124]

CONCLUSIONS

The emergence of novel drug delivery systems and its further evolution has attracted the interest of researchers in psoriasis. A wide range of efforts has been made which are mostly centered on the development of carrier-based formulations like liposomes and other colloidal range supra structures. The fundamental interest of such carriers lies on making the existing drugs more effective, safe, and patient-compliant. The studies suggest the importance of these systems for the enhancement in the skin penetration and accumulation of drug along with improved patient compliance. The unique moisturizing ability of the vesicles and its interactions through liposomal lipids with the skin lipids are the possible reason for the improvement in cutaneous transport of drugs. The problem of bulkiness of the molecules could be overcome by way of carrier interactions with the skin cells as reported in the case of cyclosporin. Besides latter, the moderation in the reactivity of the drugs such as dithranol could be of great avail by way of strategic liposomal (carrier) design.

Further, despite so much of work done on development of technique, it could not be extended sufficiently to the clinical level, which reflects a gap between the two domains of research, i.e., clinical and pharmaceutical. However, out of few isolated attempts for clinical applications, the availability of liposome-based dithranol and coal tar gel in the market exemplifies the initiation of the progress. And it needs an all round effort from different stakeholders to work out the bottleneck problems especially the cost of raw materials, scale-up stability and quality issues to ensure the availability of the products, while the establishment of clinical efficacy in psoriasis is of paramount interest.

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